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Relation of body mass index to cancer risk in 362,552 Swedish men

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Abstract
Background Obesity has been linked with increased risk for cancers of the colon, kidney, breast, endometrium and gallbladder. For other cancer sites, the relationship with obesity is less well quantified, and the effect of weight change on cancer risk is unclear.
Methods We examined the health records of 362,552 Swedish men who underwent at least one physical examination from 1971 to 1992, and were followed until death or the end of 1999. Incident cancer cases were identified by linkage to the Swedish cancer registry. Poisson regression models were used to estimate relative risks of cancer for both body-mass index (BMI) at baseline exam and, in a subgroup of 107,815 men, change in BMI after six years of follow-up, adjusting for age and smoking status.
Results Compared to men of normal weight, obese men had a significantly increased risk of all cancers combined (RR = 1.1; 95% CI = 1.0–1.2). The risks were most pronounced for esophageal adenocarcinoma (RR = 2.7; 95% CI = 1.3–5.6), renal cell carcinoma (RR = 1.8; 95% CI = 1.4–2.4), malignant melanoma (RR = 1.4; 95% CI = 1.1–1.7), and cancers of the colon (RR = 1.7; 95% CI = 1.5–2.0), rectum (RR = 1.4; 95% CI = 1.1–1.7), and liver (RR = 3.6; 95% CI = 2.6–5.0). Risk of esophageal squamous cell carcinoma was elevated for underweight men whose BMI was less than 18.5 (RR = 3.1; 95% CI = 1.1–8.3). An excess risk for cancers of the pancreas and connective tissue was observed only among nonsmokers. Compared to men whose weight remained stable, men with more than a 15% increase in BMI after six years of follow-up had an elevated risk of pancreas and renal cell cancers.
Conclusions Obesity and weight gain increase the risk for several forms of cancer in men, and underscore the need for further study into carcinogenic mechanisms and preventive interventions.

Keywords Obesity · Cancer incidence · Body mass index · Sweden

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Obesity is known to predispose to a number of cancers in certain populations, including cancers of the colon, kidney, breast, endometrium, and gallbladder [1]. Despite evidence suggesting that obesity is a risk factor for other types of cancer [1–6], the relationships have not been well quantified, particularly for uncommon cancers. In addition, weight gain has been associated in a few studies with increased risk of renal cancer, pancreas cancer, female breast cancer, and colon adenomas [7–10], but for other tumors the effect of weight gain is unclear.

In order to examine these relationships, we conducted a study of incident cancers in a large cohort of men in whom height and weight measurements were obtained at baseline examination and who were followed for up to 28 years. In a subgroup of 107,815 men

who underwent subsequent examination, we evaluated the effect of changes in body-mass index on the risk of selected cancers.

Methods

Cohort identification

The Swedish Foundation for Occupational Safety and Health of the Construction Industry (Bygghälsan) was established with the primary goal of providing preventive medical care to all workers in the construction industry, nationwide. Workers were invited to undergo health care examinations at 2–5 year intervals. Between 1971 and 1992, a total of 389,132 workers were registered in the health examination database. Since women comprised only 5% of the cohort (n = 19,418), and the numbers of cancers diagnosed during follow-up were too few for detailed evaluation, they were excluded from this analysis. Also excluded were male workers with indeterminate dates of emigration or baseline examination (n = 2,313, < 1%), men with missing baseline height or weight measurements (n = 3,097, < 1%), and men who were younger than 18 or older than 67 years of age at baseline examination (1,752, 1.3%).

Follow-up

Cohort members were followed for cancer incidence through linkage to the population-based Swedish cancer registry using the national registration number. The cancer registry was established in 1958 with over 98% completeness for case ascertainment [11]. Record linkage to the nationwide Mortality Registry provided dates of death for those who died during follow-up, and linkage to the Migration Register provided departure dates for those who emigrated. Workers were followed from date of cohort entry (date of initial examination) until date of cancer diagnosis, emigration, death, or until 31 December 1999. This study was approved by the Institutional Review Boards of all participating centers.

Statistical analyses

Incident cancers were classified according to the International Classification of Diseases (ICD), 7th revision. Height and weight were measured at baseline and at each follow-up examination. Body mass index (BMI), defined as weight in kilograms divided by height in meters squared, was calculated for each subject. Based on World Health Organization standards [12], BMI was used to categorize men as underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI ≥ 30.0). Normal weight subjects were used as a reference group for comparison. For most cancer sites, there were fewer than five cases among men in the underweight category (BMI < 18.5).

We also examined cancer risks separately among men who never smoked (n = 147,881; 40.8%), as well as across the following categories of follow-up time: < 5 years, 5 to 9.9 years, 10 to 14.9 years, and 15 or more years from baseline examination. Since hypertension has been shown to be a risk factor for renal cell cancer independent of BMI, all models for kidney and renal cell cancer were adjusted for diastolic blood pressure as a continuous variable [13]. Relative risks (RR) of cancer and 95% confidence intervals (95% CI) were estimated using Poisson regression models, adjusting for attained age grouped into 10-year intervals, attained calendar time grouped in 5-year intervals, and smoking status (non-smoker, former or current smoker at baseline). All analyses were performed using Epicure software [14]. The score test was used to test for linear trends, where BMI was entered as a continuous variable in the logistic models [15].

The main analysis was based on data from the baseline exams for the entire cohort. In a subgroup of 107,815 workers who went for follow-up exams approximately six years after their baseline exams, we investigated the association between weight change and risk for cancers that were associated with obesity and overweight at baseline. Differences in weight values between the baseline and follow-up examination measurements were used to assess the effect of changes in BMI, which was grouped into five categories: > −4%, −4 to +4%, +5 to +9%, +10 to +14%, and an increase of 15% or more. Men whose BMI was relatively unchanged at these two examinations (−4 to +4%) were used as the referent group, and all models were adjusted for BMI at baseline. In this analysis, person-years were accumulated after the sixth-year follow-up visit.

Results

The final cohort included 362,552 men (Table 1) who entered the cohort at an average age of 34.3 years. They were followed for an average of 19 years, for a cumulative total of 6,918,667 person-years. At the time of entry, 52% were current smokers or had smoked in the past. They had a mean body-mass index of 24.1 (SD = 3.2), which tended to increase with age.

Table 1 Characteristics of men in the Swedish Construction Worker Cohort

Age at entry	No. of men (%)	Follow-up, person-years	Ever smoked (%)[a]	Body Mass Index[b]
< 30 yr	172,637 (47.6)	3,168,671	42.5	23.0 (2.8)
30–39 yr	76,362 (21.1)	1,581,024	61.3	24.5 (3.0)
40–49 yr	52,212 (14.4)	1,060,265	62.9	25.4 (3.1)
50–59 yr	45,377 (12.5)	853,326	60.9	25.7 (3.2)
> = 60 yr	15,964 (4.4)	255,381	53.1	25.7 (3.2)
Overall	362,552 (100)	6,918,667	52.2	24.1 (3.2)

[a]Ever smoked includes former and current smokers at baseline examination. Since 25,527 subjects were missing smoking information, smoking was categorized as never (n = 147,881), former (n = 51,274), current (n = 137,870, and unknown (n = 25,527)

[b]Mean Body Mass Index (SD) for each age group. Body mass index is the weight in kilograms divided by the square of the height in meters

Significant trends of increasing risk associated with overweight and obesity were observed for all cancers combined, and for cancers of the colon, rectum, liver, and prostate, as well as renal cell carcinoma and malignant melanoma (Table 2). Although we saw no overall excess risk of esophageal cancer, when examined by histologic type, obese subjects had an almost 3-fold risk of esophageal adenocarcinoma. Conversely, risk of esophageal squamous cell carcinoma was reduced among overweight and obese individuals, and elevated among underweight subjects whose BMI was less than 18.5 (RR = 3.06; 95% CI 1.13–8.28) (data not shown).

The trend of increasing risk with increasing BMI for colon cancer was observed for all subsites, although it was not statistically significant for tumors of the descending colon. The majority of liver cancers were designated as hepatocellular carcinoma, followed by cholangiocarcinoma, with both types showing an increasing risk with increasing BMI. Obesity-related risk for kidney cancer was confined to renal cell carcinoma, with no increased risk for cancer of the renal pelvis. Obese men had a marginally significant increase in risk of connective tissue cancers, while inverse trends in BMI-related risk were observed for noncardia gastric cancer and lung cancer, as well as esophageal squamous cell carcinoma.

For cancer sites where elevated or decreased risks were noted, and where the numbers of cases permitted, we examined cancer risks separately among 147,881 men who never smoked (Table 3). The trends in BMI-related risk were more conspicuous for all cancers and most sites, including renal cell cancer and cancers of the colon, rectum, liver, and connective tissue. With smokers removed from the analysis, the trend in risk for pancreas cancer became statistically significant ($p < 0.05$), with a significantly elevated risk among obese men (RR = 1.80; 95% CI = 1.01–3.19). In addition, the reduced risk initially observed for lung cancer disappeared among nonsmokers.

To examine risk over time, we stratified the analyses into < 5, 5–9.9, 10–14.9, and 15 or more years of follow-up from baseline examination (data not shown). Risk estimates remained stable across all periods of follow-up, with the majority of cancers occurring 10 or more years after baseline examination. We also evaluated the BMI-related risks separately for men in white collar (i.e., office or managerial positions) and blue collar jobs within the construction industry, and found little difference in risks (data not shown). Lastly, we conducted the analyses treating BMI as a continuous variable. Cancer sites that were significantly elevated across BMI categories were also significantly elevated when BMI was examined continuously.

In a subgroup of 107,815 workers who had follow-up exams approximately 6 years after their baseline exams, we investigated the association between weight change and the trends in risk for cancers that were associated with elevated BMI at baseline (Table 4). After adjustment for baseline BMI, the risks for all cancers and several sites tended to increase with further increases in BMI over time, including renal cell cancer and cancers of liver, pancreas, and lung, although none of the trends reached statistical significance. Of note, subjects whose BMI increased more than 15% since baseline examination had more than a twofold risk of pancreas cancer (RR = 2.67; 95% CI = 1.22–5.84) and 60% excess risk for renal cell cancer (RR = 1.66; 95% CI = 0.77–3.59). Overall, weight loss was not significantly related to cancer risk (RR = 1.07; 95% CI = 0.98–1.17). However, a significant excess risk was observed for pancreas cancer (RR = 1.9; 95% CI = 1.03–3.77; n = 20 cases) (data not shown in table), with risk mainly confined to the first five years of follow-up.

Table 2 Relative risks (RR) and 95% confidence intervals (95% CI) for cancer according to body mass index[a,b]

Cancer site (ICD7)	Normal weight cases	Overweight (BMI 25.0–29.9)			Obese (BMI > 30.0)			*p*-test for trend
		Cases	RR	95% CI	Cases	RR	95% CI	
All cancers (140–207)	12,103	10,341	1.01	0.98–1.04	1,805	1.10	1.04–1.15	<0.01
Esophagus (150)	184	110	0.76	0.59–0.96	26	1.14	0.76–1.73	0.37
Adenocarcinoma	34	38	1.58	0.98–2.53	10	2.72	1.33–5.55	<0.01
Squamous cell carcinoma[c]	134	57	0.53	0.39–0.72	13	0.77	0.43–1.36	<0.01
Stomach (151)	666	531	0.87	0.77–0.97	84	0.83	0.66–1.05	<0.05
Cardia (151.0)	108	105	1.16	0.88–1.52	16	1.09	0.64–1.85	0.40
Other (151.x)	558	426	0.81	0.72–0.92	68	0.78	0.61–1.01	<0.01
Small intestine (152)	61	69	1.44	1.01–2.04	9	1.16	0.58–2.36	0.28
Colon (153)	763	842	1.24	1.12–1.37	190	1.74	1.48–2.04	<0.001
Cecum/ascending (153.0)	263	277	1.22	1.02–1.44	47	1.29	0.94–1.77	<0.05
Transverse (153.1)	118	114	1.13	0.87–1.47	32	2.00	1.34–2.96	<0.01
Descending (153.2)	35	34	1.13	0.70–1.83	8	1.60	0.73–3.47	0.14
Sigmoid (153.3)	226	293	1.37	1.15–1.64	62	1.77	1.33–2.35	<0.001
Rectum (154)	626	610	1.08	0.96–1.21	126	1.36	1.13–1.66	<0.01
Liver/intrahepatic bile ducts (155.0)	115	126	1.29	1.00–1.68	56	3.62	2.62–5.00	<0.001
Hepatocellular carcinoma	73	90	1.45	1.06–1.98	31	3.13	2.04–4.79	<0.001
Cholangiocarcinoma	16	15	1.14	0.56–2.32	8	3.78	1.59–8.96	<0.01
Adenocarcinoma	20	17	1.00	0.51–1.93	12	4.38	2.09–9.14	<0.001
Gallbladder (155.1)	53	45	0.93	0.62–1.39	11	1.40	0.73–2.70	>0.5
Pancreas (157)	352	289	0.95	0.82–1.12	57	1.16	0.87–1.53	>0.5
Larynx (161)	149	97	0.85	0.66–1.10	17	0.94	0.57–1.56	>0.35
Lung, trachea and bronchus (162)	1,638	1,040	0.80	0.74–0.87	153	0.74	0.63–0.88	<0.001
Connective tissue (197)	105	82	1.07	0.79–1.44	20	1.64	1.01–2.68	0.07
Malignant melanoma (190)	555	454	1.27	1.12–1.45	74	1.35	1.06–1.73	<0.001
Prostate (177)	3,003	3,160	1.06	1.01–1.12	528	1.09	0.99–1.19	< 0.05
Bladder (181)	1,066	836	0.94	0.86–1.03	128	0.91	0.76–1.09	0.21
Kidney (180)[d]	444	448	1.23	1.08–1.42	94	1.61	1.27–2.04	<0.001
Renal cell (180.0)[d]	358	376	1.28	1.10–1.49	86	1.82	1.41–2.35	<0.001
Renal pelvis (180.1)[d]	52	34	0.93	0.47–1.84	6	1.18	0.27–5.14	>0.5
Brain (193.0)	519	353	1.03	0.89–1.18	46	0.86	0.63–1.16	>0.5
Thyroid (194)	89	73	1.24	0.90–1.71	9	0.98	0.49–1.96	0.48
Non-Hodgkin lymphoma (200, 202)	564	442	1.02	0.89–1.16	71	1.02	0.80–1.31	>0.5
Hodgkin disease (201)	134	61	0.90	0.66–1.24	16	1.59	0.94–2.71	0.34
Multiple myeloma (203)	231	201	0.96	0.79–1.16	20	0.58	0.37–0.93	0.06
Leukemia (204–207)	399	310	0.97	0.83–1.13	58	1.12	0.85–1.48	>0.5
Chronic lymphocytic (204.1)	164	179	1.20	0.97–1.49	24	0.98	0.63–1.51	0.36
Acute myeloid (205.0)	149	96	0.84	0.64–1.09	22	1.19	0.76–1.88	>0.5
Chronic myeloid (205.1)	64	25	0.58	0.36–0.94	9	1.35	0.66–2.74	>0.5

[a]Adjusted for attained age (10-year intervals) and calendar year (5-year intervals), and smoking status (never, former, current, unknown), and relative to normal weight subjects

[b]Risk relative to a reference group of men with a normal BMI (18.5–24.9)

[c]For those in the underweight category where BMI < 18.5: RR = 3.06; 95% CI 1.13–8.28) 4 cases

[d]Adjusted for diastolic blood pressure (continuous)

Discussion

In this prospective study of Swedish construction workers, we found that elevated BMI was associated with significant trends of increased risk for all cancers combined and for several forms of cancer, including esophageal adenocarcinoma, renal cell carcinoma, melanoma, and cancers of the colon, rectum, liver, and prostate. These trends became more pronounced for most cancers when current and former smokers were excluded from the analysis.

Obesity is an established risk factor for adenocarcinomas of the esophagus, colon and kidney [1], while relationships reported with other cancers have been less consistent. Esophageal adenocarcinoma, which is rapidly increasing in incidence in the U.S. and western Europe [16], has been linked to obesity in case–control studies utilizing self-reported body weight [16–19] as well as prospective studies based on height and weight measurements [20, 21]. Although mechanisms are unclear, obesity predisposes to gastroesophageal reflux disease and Barrett's esophagus, a metaplastic

Table 3 Relative risks (RR) and 95% confidence intervals (95% CI) for cancer according to body mass index among 147,881 subjects who never smoked[a]

Cancer site	Normal weight cases	Overweight (BMI 25.0–29.9)			Obese (BMI > 30.0)			*p*-test for trend
		Cases	RR	95% CI	Cases	RR	95% CI	
All cancers	2,736	2,859	1.11	1.05–1.17	531	1.26	1.14–1.38	< 0.001
Colon	218	272	1.24	1.03–1.49	70	1.94	1.48–2.56	< 0.001
Rectum	172	159	0.93	0.75–1.16	48	1.70	1.23–2.35	0.01
Liver	21	28	1.38	0.77–2.46	16	4.83	2.48–9.40	< 0.001
Pancreas	46	64	1.22	0.83–1.79	16	1.80	1.01–3.19	< 0.05
Renal cell[b]	67	105	1.94	1.21–3.09	25	3.49	1.40–8.69	< 0.001
Prostate	811	1,051	1.12	1.02–1.22	167	1.06	0.90–1.25	0.11
Lung	54	63	1.17	0.81–1.70	10	1.11	0.56–2.20	0.47
Connective tissue	36	23	1.09	0.64–1.86	11	2.94	1.45–5.94	< 0.01
Melanoma	233	176	1.13	0.92–1.38	31	1.31	0.90–1.92	0.11

[a]Adjusted for attained age (10-year intervals) and calendar year (5-year intervals), and relative to normal weight subjects

[b]Adjusted for diastolic blood pressure (continuous)

precursor to esophageal adenocarcinoma [16, 22]. On the other hand, populations at high risk for esophageal squamous cell carcinoma are generally underweight, with risk increasing as BMI decreases [23]. Residual confounding by alcohol consumption, a major risk factor for esophageal squamous cell cancer [23, 24], may have contributed to the excess risk among the underweight individuals in this study and others. We were not able to confirm previous observations relating obesity to gastric cardia adenocarcinoma [16, 18, 20, 25], and reasons for the inverse association we observed for noncardia gastric cancers are unclear.

Although obesity is an established risk factor for colon cancer [1, 3, 4, 26–30], results for colon subsites have been mixed. Some studies have reported stronger associations between high BMI and cancer or adenomas of the descending colon than for the ascending colon [31, 32], while others have not [33]. Our results suggest that obesity is a risk factor for cancers arising from all subsites of the colon.

The association between obesity and rectal cancer has been less consistent [29, 34–36]. In a cohort study of patients hospitalized for obesity in Sweden, risk of rectal cancer was non-significantly elevated among men but not among women [3], while obesity was associated with excess mortality from rectal cancer in a U.S. cohort study [5]. More recently, overweight and obesity were associated with excess risk of rectal cancer in a Canadian case–control study utilizing self-reported body weight [26]. Despite evidence for an excess risk of colon and rectal cancers among overweight and obese men in our study, there was no

Table 4 Relative risks (RR) and 95% confidence intervals (95% CI) for cancer associated with changes in BMI among 107,815 subjects with a 6-year follow-up exam[a,b]

Cancer	−4 to +4.9% (reference)	+5 to + 9.9%			+10 to + 14.9%			More than + 15%			*p*-value for trend
	No. with cancer	No. with cancer	RR	95%CI	No. with cancer	RR	95%CI	No. with cancer	RR	95%CI	NS
All cancers	4,268	1,450	1.02	0.96–1.08	433	1.00	0.90–1.11	163	1.12	0.96–1.31	>0.5
Esophageal adenocarcinoma	19	3	0.44	0.13–1.49	5	2.24	0.81–6.21	1	1.21	0.16–9.45	>0.5
Colon	333	99	0.95	0.76–1.19	31	1.05	0.72–1.52	9	0.96	0.49–1.87	>0.5
Rectum	244	71	0.89	0.68–1.16	23	0.99	0.64–1.52	6	0.81	0.36–1.83	0.31
Liver	33	15	1.43	0.77–2.65	5	1.72	0.66–4.48	2	2.26	0.53–9.59	>0.5
Pancreas	86	41	1.45	1.00–2.11	13	1.53	0.85–2.77	7	2.67	1.22–5.84	>0.5
Lung	469	148	0.95	0.79–1.14	50	1.06	0.79–1.42	25	1.75	1.17–2.64	>0.5
Connective tissue	39	16	1.08	0.60–1.95	5	0.96	0.37–2.49	2	0.96	0.23–4.10	>0.5
Prostate	1,281	417	1.09	0.98–1.22	97	0.93	0.75–1.14	22	0.75	0.49–1.15	>0.5
Renal cell[c]	127	48	1.13	0.81–1.58	20	1.55	0.96–2.51	7	1.66	0.77–3.59	>0.5

[a]Adjusted for attained age (10-year intervals) and calendar year (5-year intervals), smoking status (never, former, current), and BMI group at baseline examination

[b]Subjects who were underweight at baseline (BMI < 18.5) were excluded from this analysis

[c]Adjusted for diastolic blood pressure (continuous)

relation to weight gain as suggested by some studies of colorectal tumors, especially adenomas [37, 38]. Our data on weight gain, however, were limited to the first few years of follow-up.

The excess risk of renal cell cancer among individuals with elevated BMI is well-documented [2–4, 26, 39–41]. Obese men in our study had a significantly increased risk for renal cell cancer that was more pronounced among non-smokers. This finding is similar to results from a Norwegian cohort study based on measurement data [42]. Our findings also indicate that increases in BMI over time further elevate the risk of renal cell carcinoma, as previously reported in an earlier analysis of kidney cancer in this cohort [13].

Results from previous studies of obesity and prostate cancer have been inconsistent [1, 43–45]. Although the trend in risk observed in our study achieved statistical significance, the magnitude of excess risk was small for both overweight and obese men. In an earlier investigation involving a subset of our cohort, a small but significant trend of increasing risk was observed for BMI and prostate cancer mortality but not incident tumors [46], suggesting that obesity may predispose to more aggressive forms of prostate cancer [47–49].

While there was no overall increase in risk of pancreas cancer among obese men in our study, an elevated risk was seen among nonsmoking obese men. Obesity has been associated with pancreas cancer in some studies [3–6, 26, 50–53], but not in others [54–57]. Evidence for a positive relationship is provided by a pooled analysis of data from two prospective studies suggesting a 50–70% increase in risk among obese individuals [53], and from a meta-analysis involving 6,391 cases of pancreas cancer [58]. We also observed a greater than twofold increased risk of pancreas cancer among subjects whose BMI increased more than 15% since baseline examination. In a recent cohort study based on the Swedish Twin Registry, adult weight gain was associated with a 50% increased risk of pancreas cancer [8]. While a U.S. cohort study reported no overall association between adult weight gain and pancreas cancer risk, a higher risk was associated with central weight gain (e.g., chest, shoulders or waist) compared to peripheral weight gain [52]. The increased risk of pancreas cancer associated with weight loss in our cohort was likely due to preclinical disease, since the excess risk was limited to cases diagnosed during the period soon after weight loss measurement.

Obesity has been linked to primary liver cancer in both incidence [3, 4, 6] and mortality [5] studies. We found a dose-response trend of higher risk with increasing BMI, and the risk persisted among non-smokers. The mechanism linking obesity to liver cancer is unclear, but may act through progression of non-alcoholic fatty liver disease, and by promoting insulin resistance and metabolic syndrome [59–63].

The association we observed between BMI and melanoma risk has been inconsistent in previous studies [6, 64–71], suggesting the need for further work to disentangle the potential effects of physical inactivity [70], diet [65, 72–74], body surface area [64, 70], melanocyte count [70, 75], and sex hormones [73, 76–80], which have been associated with melanoma risk in some studies. The incidence of connective tissue cancers was also elevated among obese men in our study, which is consistent with previous cohort studies in the U.S. [6] and Sweden [3] and a case–control study in Italy [81]. Although some studies have suggested a relationship between obesity and risk of hematopoietic cancers [3, 26, 82–84], we did not find an obesity-related risk for either leukemia or lymphoma.

This cohort study has advantages over many previous studies of obesity and cancer risk. All analyses were based on actual measurements of height and weight at baseline and follow-up examinations, thus reducing the possibility for misclassification of BMI status. We were able to achieve nearly complete follow-up of the cohort for incident cancers by linkage to the population-based Swedish cancer registry, thus minimizing potential ascertainment bias. Analysis of incident cancer cases also minimized potential biases that may occur in mortality-based studies, such as differences in cancer survival and incomplete reporting of causes of death.

Our relatively homogeneous cohort of construction workers in Sweden also reduced the potential for confounding by other unmeasured factors, including socioeconomic status [85] and lifestyle factors such as physical activity and diet [86–89]. Support for the notion that SES is not an important confounding factor in this cohort was the similarity in obesity-related risks for white collar and blue collar workers in the Swedish construction industry. Physical activity levels on the job also should be relatively homogeneous within blue collar and white collar jobs. Although smoking and BMI tend to be inversely associated [90], risk estimates did not substantially change when the analysis was restricted to men who never smoked.

Despite the large cohort size and long duration of follow-up, the number of cases was limited for some cancer sites, particularly among the subgroup of men who had a 6-year follow-up examination. Therefore, some findings may be due to chance because of small numbers and multiple comparisons. Information on long-term changes in BMI measurements was not available since the measurements were taken only at

two points in time (i.e., at baseline and for a subset of men at the sixth year follow-up examination). However, the excess risks observed with increasing BMI remained relatively stable across years of follow-up, supporting the validity of our observations. In addition, we were unable to examine the role of anthropometric indices such as waist-to-hip ratio, which may be a better indicator of adiposity as a cancer risk factor.

Several biologic mechanisms may contribute to the association between obesity and risk of various cancers [91]. Metabolic changes associated with obesity include impaired glucose tolerance, hyperlipidemia, insulin resistance and hyperinsulinemia, as well as altered levels of circulating hormones and insulin-like growth factor-I and its binding proteins [92–94]. In addition, inflammatory mediators such as cytokines and prostaglandins, which are secreted by fat cells, may contribute to the obesity-related risks of certain cancers [95, 96].

In summary, our large cohort study of Swedish construction workers confirmed previous studies that overweight and obese individuals have a higher risk of esophageal adenocarcinoma, renal cell cancer, and cancers of the colon (all subsites), rectum, and liver. In addition, our findings suggest that obesity may be a risk factor for melanoma and connective tissue cancers, and that weight gain further increases the risk of some cancers, particularly pancreatic and renal cell cancers. Given the increasing prevalence of obesity worldwide, there is an urgent need to understand the causal pathways by which obesity and weight gain increase the risk of various forms of cancer, and to develop preventive measures.

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References

1. IARC handbooks of cancer prevention (2002) Weight control and physical activity, vol 6. International Agency for Research on Cancer, Lyon, France
2. Bianchini F, Kaaks R, Vainio H (2002) Overweight, obesity and cancer risk. Lancet Oncol 3:565–574
3. Wolk A, Gridley G, Svensson M, et al (2001) A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 12:13–21
4. Moller H, Mellemgaard A, Lindvig K, Olsen JH (1994) Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer 30A:344–350
5. Calle E, Rodriguez C, Walker-Thurmond K, Thun MJ. (2003) Overweight, obesity and mortality from cancer in a prospectively studied cohort of US adults. N Engl J Med 348:1625–1638
6. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni JF Jr. (2004) Obesity and cancer risk among white and black United States veterans. Cancer Causes Control 15:35–44
7. Bird CL, Frankl HD, Lee ER, Haile RW (1998) Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am J Epidemiol 147:670–680
8. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting, Permert J (2002) Lifestyle factors and pancreatic risk: a cohort study. Int J Cancer 98:480–482
9. Lindblad P, Wolk A, Bergstrom R, Persson I, Adami HO (1994) The role of obesity and weight fluctuations in the etiology of renal cell cancer: a population-based case–control study. Cancer Epidemiol Biomarkers Prev 3:631–639
10. Ballard-Barbash R, Schatzkin A, Taylor PR, Kahle LL (1990) Association of change in body mass with breast cancer. Cancer Res 50:2152–2155
11. Mattsson B, Rutqvist LE, Wallgren A (1985) Undernotification of diagnosed cancer cases to the Stockhom Cancer Registry. Int J Epidemiol 14:64–69
12. Report of a WHO consultation. Obesity: preventing, managing the global epidemic. 894:i–xii, 1–253. 2000. World Health Organization. World Health Organ Tech Rep Ser
13. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B (2000) Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 343:1305–1311
14. Preston DL, Lubin JH, Pierce DA, McConney ME (1996) Epicure User's Guide. HiroSoft International Corporation, Seattle, WA
15. Breslow NE, Day NE (1987) The design and analysis of cohort studies. In: International Agency for Research on Cancer, ed. In: Statistical methods in cancer research. Lyon
16. Chow W., Blot W., Vaughan TL, et al (1998) Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 90:150–155
17. Wu AH, Wan P, Bernstein L (2001) A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus. Cancer Causes Control 12:721–732
18. Lagergren J, Bergstrom R, Nyren O (1999) Association between body mass index and adenocarcinoma of the esophagus and gastric cardia. Arch Intern Med 130:883–890
19. Brown LM, Swanson CA, Gridley G, et al (1995) Adenocarcinoma of the esophagus: role of obesity and diet. J Natl Cancer Inst 87:104–109
20. Lindblad M, Garcia A, Lagergren J (2005) Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nest case–control study. Cancer Causes Control 16:285–294
21. Engeland A, Tretli S, Bjorge T (2004) Height and body mass index in relation to esophageal cancer; 23-year follow-up of two million Norwegian mean and women. Cancer Causes Control 15:837–843
22. Lagergren J (2005) Adenocarcinoma of the esophagus: what exactly is the size of the problem and who is at risk? Gut 54(Suppl I):i1–i5
23. Brown LM, Hoover RN, Greenberg RS, et al (1994) Are racial differences in squamous cell esophageal cancer explained by alcohol and tobacco use? J Natl Cancer Inst 86:1340–1345

24. Brown LM, Hoover RN, Silverman D, et al (2001) Excess incidence of squamous cell esophageal cancer among US black men: role of social class and other risk factors. Am J Epidemiol 153:114–122
25. Vaughan TL, Davis S, Kristal A, Thomas DB (1995) Obesity, alcohol and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidem Biomarkers Prev 4:85–92
26. Pan SY, Johnson KC, Ugnat AM, Wen SW, Mao Y, Canadian Cancer Registries Epidemiology Research Group (2004) Association of obesity and cancer risk in Canada. Am J Epidemiol 159:259–268
27. Russo A, Franceschi S, La Vecchia C, et al (1998) Body size and colorectal-cancer risk. Int J Cancer 78:161–165
28. Ford ES (1999) Body mass index and colon cancer in a national sample of adult US men and women. Am J Epidemiol 150:390–398
29. Gerhardsson De Verdier M, Hagman U, Steineck G, Rieger A, Norell SE (1990) Diet, body mass and colorectal cancer: a case-referent study in Stockholm. Int J Cancer 46:832–838
30. Kreger BE, Anderson KM, Shatzkin A, Splansky GL (1992) Serum cholesterol level, body mass index, and the risk of colon cancer. Cancer 70:1038–1043
31. Honjo S, Kono S, Shinchi K, et al (1995) The relation of smoking, alcohol use and obesity to risk of sigmoid colon and rectal adenomas. Jpn J Cancer Res 86:1019–1026
32. Le Marchand L, Wilkens LR, Mi MP (1992) Obesity in youth and middle age and risk of colorectal cancer in men. Cancer Causes Control 3:349–354
33. Graham S, Marshall J, Haughey B, et al (1988) Dietary epidemiology of cancer of the colon in western New York. Am J Epidemiol 128:490–503
34. Slattery ML, Caan BJ, Benson J, Murtaugh M (2003) Energy balance and rectal cancer: an evaluation of energy intake, energy expenditure, and body mass index. Nutr Cancer 166–171
35. Mao Y, Pan S, Wen SW, Johnson KC, Canadian Cancer Registries Epidemiology Research Group (2003) Physical inactivity, energy intake, obesity and the risk of rectal cancer in Canada. Int J Cancer 105:831–837
36. Giacosa A, Franceschi S, La Vecchia C, Favero A, Andreatta R (1999) Energy intake, overweight, physical exercise and colorectal cancer risk. Eur J Cancer Prev 8:S53–S60
37. Kono S, Handa K, Hayabuchi H, et al (1999) Obesity, weight gain and risk of colon adenomas in Japanese men. Jpn J Cancer Res 90:805–811
38. Bird CL, Frankl HD, Lee ER, Haile RW (1998) Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. Am J Epidemiol 147:670–680
39. Whittemore AS, Paffenbarger RS, Anderson K, Lee JE (1985) Early precursors of site-specific cancers in college men and women. J Natl Cancer Inst 74:43–51
40. Shapiro JA, Williams MA, Weiss NS (1999) Body mass index and risk of renal cell carcinoma. Epidemiology 10:188–191
41. Moore LE, Wilson RT, Campleman SL (2005) Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. Cancer Invest 23:240–255
42. Bjorge T, Tretli S, Engeland A (2004) Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women. Am J Epidemiol 160:1168–1176
43. Presti JC Jr (2005) Obesity and prostate cancer. Curr Opin Urol 15:13–16
44. Nomura AM (2001) Body size and prostate cancer risk. Epidemiol Rev 126–131
45. Engeland A, Tretli S, Bjorge T (2003) Height, body mass index, and prostate cancer: a follow-up of 950,000 Norwegian men. Br J Cancer 89:1237–1242
46. Andersson SO, Wolk A, Bergstrom R, et al (1997) Body size and prostate cancer: a 20-year follow-up study among 135,006 Swedish construction workers. J Natl Cancer Inst 89:385–389
47. Amling CL (2005) Relationship between obesity and prostate cancer. Curr Opin Urol 15:167–171
48. Giovanucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC (1997) Height, body weight and risk of prostate cancer. Cancer Epidem Biomarkers Prev 6:557–563
49. Freedland SJ, Giovannucci E, Platz EA (2006) Are findings from studies of obesity and prostate cancer really in conflict? Cancer Causes Control 17:5–9
50. Larsson SC, Permert J, Hakansson N, Naslund I, Bergkvist L, Wolk A (2005) Overall obesity, abdominal adiposity, diabetes and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. Br J Cancer 93:1310–1315
51. Silverman DT, Swanson CA, Gloria G, et al (1998) Dietary and nutritional factors and pancreatic cancer: a case–control study based on direct interviews. J Natl Cancer Inst 90:1710–1719
52. Patel AV, Rodriguez C, Bernstein L, Chao A, Thun MJ, Calle EE (2005) Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. Cancer Epidemiol Biomarkers Prev 14:459–466
53. Michaud DS, Giovanucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS (2001) Physical activity, obesity, height, and risk or pancreatic cancer. JAMA 286:921–929
54. Lee IM, Sesso HD, Oguma Y, Paffenbarger RS (2003) Physical activity, body weight, and pancreatic cancer mortality. Br J Cancer 88:679–683
55. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D (2005) A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). Cancer Causes Control 13:417–426
56. Howe GR, Jain M, Miller AB (1990) Dietary factors and risk of pancreatic cancer: results of a Canadian population-based case–control study. Int J Cancer 45:604–608
57. Friedman GD, Van Den Eeden SK (1993) Risk factors for pancreatic cancer: an exploratory study. Int J Epidemiol 22:30–37
58. Berrington de Gonzalez A, Sweetland S, Spencer E (2003) A meta-analysis of obesity and the risk of pancreatic cancer. Br J Cancer 89:519–523
59. Qian Y, Fan JG (2005) Obesity, fatty liver and liver cancer. Hepatobiliary Pancreat Dis Int 4:173–177
60. Cladwell SH, Crespo DM, Kang HS, As-Osaimi AMS (2004) Obesity and hepatocellular carcinoma. Gastroenterology 127:S97–S103
61. Yang SQ, Lin HZ, Hwang J, Chacko VP, Diehl AM (2001) Hepatic hyperplasia and noncirrhotic fatty livers: is obesity-related hepatic steatosis a premalignant condition. Cancer Res 61:5016–5023
62. Angelico F, Del Ben M, Conti R, et al (2003) Non-alcoholic fatty liver syndrome: a hepatic consequence of common metabolic diseases. J Gastroenterol Hepatol 18:588–594
63. Pagano G, Pacini G, Gambino R, et al (2002) Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology 35:367–372
64. Gallus S, Naldi L, Martin L, Martinelli M, Carlo La Vecchia on behalf of the Oncology Study Group of the Italian Group for Epidemiologic Research in Dermatology (GISED) (2006) Anthropometric measures and risk of cutaneous malignant melanoma: a case–control study from Italy. Melanoma Res 16:83–87

65. Kirkpatrick CS, White E, Lee JA (1994) Case–control study of malignant melanoma in Washington State. II. Diet, alcohol, and obesity. Am J Epidemiol 139:869–880
66. Holman CD, Armstrong BK, Heenan PJ (1984) Cutaneous malignant melanoma in women: exogenous sex hormones and reproductive factors. Br J Cancer 50:673–680
67. Le MG, Cabanes PA, Desvignes V, Chanteau MF, Mlika N, Avril MF (1992) Oral contraceptive use and risk of cutaneous malignant melanoma in a case–control study of French women. Cancer Causes Control 3:199–205
68. Gallagher RP, Elwood JM, Hill GB, Coldman AJ, Threlfall WJ, Spinelli JJ (1985) Reproductive factors, oral contraceptives and risk of malignant melanoma in women: Western Canada Melanoma study. Br J Cancer 52:901–907
69. Osterlind A, Tucker MA, Stone BJ, Jensen OM (1988) The Danish case–control study of cutaneous malignant melanoma. Int J Cancer 42:821–824
70. Shors AR, Solomon C, McTiernan A, White E (2001) Melanoma risk in relation to height, weight and exercise (United States). Cancer Causes Control 12:599–606
71. Thune I, Olsen A, Albrektsen G, Tretli S (1993) Cutaneous malignant melanoma: association with height, weight and body-surface area. A prospective study in Norway. Int J Cancer 55:555–561
72. Millen AE, Tucker MA, Hartge P, et al (2004) Diet and melanoma in a case–control study. Cancer Epidemiol Biomarkers Prev 13:1042–1051
73. Osterlind A, Tucker MA, Stone BJ, Jensen OM (1988) The Danish case–control study of cutaneous malignant melanoma. III. Hormonal and reproductive factors in women. Int J Cancer 42:821–824
74. Veierod MB, Thelle DS, Laake P (1997) Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. Int J Cancer 71:600–604
75. Snell RS, Bischitz PG (1960) The effect of large doses of estrogen and progesterone on melanin pigmentation. J Invest Dermatol 35:75–82
76. Armstrong BK, Englund A (1996) Cutaneous malignant melanoma. In: Schottenfield D, Fraumeni JF Jr. (eds) New York, NY: Oxford University Press, pp 1282–1312
77. Beral V, Evans S, Shaw H (1984) Oral contraceptive use and malignant melanoma in Australia. Br J Cancer 50:681–685
78. Feskanich D, Hunter DJ, Willett WC, et al (1999) Oral contraceptive use and risk of melanoma in premenopausal women. Br J Cancer 81:918–923
79. Holly EA, Cress RD, Ahn DK (1995) Cutaneous melanoma in women. III. Reproductive factors and oral contraceptive use. Am J Epidemiol 141:943–950
80. Karagas MR, Stukel TA, Dykes J, et al (2002) A pooled analysis of 10 case–control studies of melanoma and oral contraceptive use. Br J Cancer 86:1085–1092
81. Tavani S, Soler M, La Vecchia C, Negri E, Gallus S, Franceschi S (1999) Body weight and risk of soft-tissue sarcoma. Br J Cancer 81:890–892
82. Cerhan JR, Janney CA, Vachon CM, et al (2002) Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. Am J Epidemiol 156:527–535
83. Holly EA, Lele C, Bracci PM, McGrath MS (1999) Case–control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol 150:375–389
84. Estey E, Thall P, Kantarjian H, Pierce S, Kornblau S, Keating M (1997) Association between increased body mass index and a diagnosis of acute promyelocytic leukemia in patients with acute myeloid leukemia. Leukemia 11:1661–1664
85. Sobal J, Stunkard AJ (1989) Socioeconomic status and obesity: a review of the literature. Psychol Bull 105:260–275
86. Oliveria SA, Christos PJ (1997) The epidemiology of physical activity and cancer. Ann NY Acad Sci 29:79–90
87. Tymchuk CN, Tessler SB, Aronson WJ, Barnard WJ (1998) Effects of diet and exercise on insulin, sex-hormone binding globulin, and prostate-specific antigen. Nutr Cancer 31:127–131
88. Key TJ, Allen NE, Spencer EA, Travis RC (2002) The effect of diet on risk of cancer. Lancet 360:861–888
89. La Vecchia C (1994) Dietary fat, obesity and cancer. In: Hill M, Giacosa A, Caygill C (eds) Epidemiology of diet and cancer. Ellis Horwood Limited, New York, pp 277–291
90. Molarius A, Seidell JC, Kuulasmaa K, Dobson AJ, Sans S (1997) Smoking and relative body weight: an international perspective from the WHO MONICA project. J Epidemiol Community Health 51:252–560
91. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nature Rev 4:579–591
92. Giovanucci E (1999) Insulin-like growth factor-1 and binding protein-3 and risk of cancer. Horm Res 51:34–41
93. Kahn BB, Flier JS (2000) Obesity and insulin resistance. J Clin Invest 106:473–481
94. Marchav S (1998) The haematopoietic effects of growth hormone and insulin-like growth factor-I. J Ped Endocrinol Metab 11:677–685
95. Cottam DR, Mattar SG, Barinas-Mitchell E, et al (2004) The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obesity Surgery 14:589–600
96. Shacter E, Weitzman SA (2002) Chronic inflammation and cancer. Oncology 16:217–229